Interventional Cardiology

Sirolimus-eluting coronary stents in small vessels

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Background This prospective multicenter study compared angiographic in-lesion late lumen loss in de novo native coronary artery lesions (vessel diameter range 2.25-2.75 mm, length range ≥15 to ≤30 mm) 8 months after the implantation of a sirolimus-eluting stent with that of similar vessels with the same drug-eluting stent or a bare stent of the SIRIUS study (historical controls).

Methods and Results One hundred one patients (study group) were matched and compared with 323 patients receiving the bare stent (bare control group) and with 350 receiving the Cypher stent (Cypher control group) in the SIRIUS trial. Mean in-lesion late loss in the study group was lower than that in the bare control group (0.20 versus 0.76 mm, P < .0001) and not inferior to that in the Cypher control group (0.27 mm, P = .3). Adverse event rates (death and myocardial infarction) were similar between groups. At 8 months, target lesion revascularization rates were 0% in the study group, 13.2% in the bare control group (P < .001), and 4.6% in the Cypher control group (P = .03).

Conclusions The Cypher Bx Velocity stent was confirmed to be superior to the bare Bx Velocity stent in small coronary vessels in terms of in-lesion late loss 8 months after implantation. (Am Heart J 2006;151:1019.e1-1019.e7.)

Rates of angiographic restenosis and target lesion revascularization (TLR) were found to be higher in small vessels (<2.5 mm in diameter) than in larger vessels 6 months after percutaneous transluminal coronary angioplasty or stenting1,2 and 1 year after stenting.3 Predictors of small vessel restenosis are diabetes, complex lesions, and long lesions.1,4,5 Although restenosis has not been conclusively linked to mortality, it can adversely affect quality of life.6 Stents reduce restenosis by preventing recoil, but tissue growth renarrows the lumen significantly in approximately 20% of patients.7-12 Small vessel stenting has shown some advantages over balloon angioplasty in randomized and nonrandomized trials but a higher risk for restenosis as compared with larger vessels.13-17

In recent years, stents eluting sirolimus or taxol have attenuated vascular hyperproliferation18-25. Sirolimus prevents neointimal proliferation.26,27 The Cypher (sirolimus-eluting Bx Velocity) stent was compared with the bare Bx Velocity stent in the SIRIUS study (1058 patients) with TLR as the primary end point. Significant reductions (P < .001) in TLR were demonstrated both at 9 months postprocedure (4% versus 17%, respectively) and 12 months later (5% versus 20%, respectively).3 Similar results were obtained by recent studies on the implantation of sirolimus-eluting stents in small vessels.28-30

The small vessel tercile analysis of the SIRIUS Trial revealed that most in-segment restenoses and revascularizations in the sirolimus group occurred in the smallest vessel tercile (mean diameter 2.3 mm). The respective in-segment binary restenoses were 18.6% in the Cypher SIRIUS arm and 42.9% in the bare SIRIUS arm versus 1.9% and 30.2%, respectively, in the large vessel group (mean diameter 3.3 mm).

The purpose of this study was to assess the effectiveness of the Cypher stent in reducing in-lesion late loss in de novo native coronary artery lesions in small vessels (diameter range 2.25-2.75 mm). Data for the patients were compared with those for historical control subjects (ie, matched patients in the small vessel tercile of the SIRIUS study), which also allowed an assessment of standardizing and controlling procedural aspects of stenting.
Methods

The study was approved by independent ethics committees and conducted in accordance with Good Clinical Practice, local regulations, and the Declaration of Helsinki. Patients gave their signed consent after the nature of the study had been disclosed to them.

All patients were treated with the Cypher stent. The study used adapted stenting techniques to minimize balloon trauma and ensure full coverage of the lesion according to lessons learned from the SIRIUS trial. In addition, the study looked into the efficacy of the treatment by comparing intravascular ultrasound (IVUS) images after stent implantation with those at 8 months. Safety was defined as absence of major adverse cardiac events (MACEs) during follow-up.

Study design and eligibility criteria

The study was performed at 9 centers in Europe, Israel, and Brazil. The patient inclusion criteria were as follows: (1) stable angina pectoris (Canadian Cardiovascular Society Classifications 1-4), unstable angina pectoris (Braunwald Classifications B and C 1-2), or documented silent ischemia; (2) a single de novo lesion in a small vessel (diameter range ≥2.25 and ≤2.75 mm, visual estimate) of a major coronary artery requiring treatment; (3) target lesion stenosis >50% and <100%; (4) target lesion length ≥15 and ≤30 mm; (5) coronary flow >TIMI 1; and (6) willingness to comply with the schedule of follow-up evaluations. Patients with the following conditions were excluded: (1) myocardial infarction within the preceding 24 hours; (2) unprotected left main coronary artery disease with ≥50% stenosis; (3) significant stenosis (>50%) proximal or distal to the target lesion; (4) ostial target lesion; (5) angiographic evidence of thrombus in the target lesion; (6) heavily calcified lesion; (7) documented left ventricular ejection fraction ≤50%; (8) excessively tortuous target lesion; and (9) target lesion involving a bifurcation with a diseased side branch ≥2.25 mm in diameter requiring treatment.

Coronary stent procedure

The recommended medication was a minimum of 100-mg acetylsalicylic acid 12 hours before the procedure and clopidogrel (loading dose 300 mg before or immediately after the procedure, followed by 75 mg once daily for at least 2 months). Heparin was given as an intravenous bolus during the procedure, with additional boluses to maintain an activated clotting time >250 seconds, and was discontinued within 12 hours. An intracoronary nitroglycerin injection preceded baseline angiography. The addition of glycoprotein IIIb/IIa inhibitors was left at the investigator’s discretion. Balloon predilatation was required (no direct stenting). The appropriate balloon size was chosen based on visual estimates of the reference vessel’s diameter. A stent system (available as 2.25, 2.50, or 2.75 mm in diameter and as 18, 23, or 30 mm in length) was selected to provide a stent/vessel ratio of 1.1:1 at nominal pressure. The stent was to be at least 3 mm longer than the balloon or the area of predilatation. The goal was to achieve an angiographic appearance of the stent expanded just outside the boundaries of the vessel. Overlap was required if >1 stent was implanted. The deployment pressure was left at the investigator’s discretion within the recommended balloon range. In the case of insufficient expansion (>30% final diameter stenosis), the stent could be postdilated with an appropriately sized balloon.

Data collection and follow-up

The study was monitored by Cordis Clinical Research Europe. Quantitative coronary angiography (QCA) was undertaken by the Brigham and Women’s Hospital Angiographic Core Laboratory (Boston, MA); IVUS analysis was performed by the IVUS Cardiovascular Core Analysis Laboratory of the Stanford University School of Medicine (Stanford, CA); and ECG analysis was conducted by the Cardiovascular Data Analysis Center of the Beth Israel Deaconess Medical Center and the Harvard Medical School (Boston, MA). An independent clinical event committee reviewed and adjudicated all major clinical events.

Follow-up data were collected at 30 days; 6, 8, and 9 months; as well as 1 year after the procedure, including an angiogram and IVUS imaging to evaluate neointimal growth and remodeling at 8 months.

Angiograms at all stages of the study included at least 2 identical orthogonal views. Intravascular ultrasound images using an automated pull-back system and standardized procedures were taken immediately after implantation of the stent and 8 months later.

Study end points

The primary end point was in-lesion late lumen loss at 8 months measured by QCA. The secondary end points assessed immediately after stent implantation comprised device success (final residual diameter stenosis <50% using the assigned device), lesion success (<50% residual stenosis using any percutaneous method), and procedure success (final diameter stenosis <50% using any percutaneous method, with no death, infarction, or TLR during the hospital stay). At 8 months, the secondary end points assessed in-stent late lumen loss, binary restenosis (≥50% diameter stenosis), in-stent minimal lumen diameter, and in-lesion minimal lumen diameter (MLD) by QCA and in-stent volume by IVUS. Secondary clinical end points up to 12 months comprised percutaneous or surgical target vessel revascularization (TVR), target vessel failure (cardiac death, myocardial infarction, or TVR), and a composite of MACEs (death, myocardial infarction, emergent bypass surgery, or repeat TLR).

Statistical analysis

The analyses included all patients treated with a Cypher stent and all patients in the SIRIUS study whose target vessel characteristics and lesion length satisfied the matching process. Patients with diabetes were matched according to reference vessel diameter (RVD) (small/large) and lesion length (short/long), resulting in 4 blocks with minima of 6 and 5 patients from the SVELTE and SIRIUS studies, respectively, and corresponding maxima of 7 and 65 patients. Patients without diabetes were matched according to RVD (small, medium-small, medium-large, large) and lesion length (short/long), resulting in 12 blocks with minima of 5 and 4 patients from this study and the SIRIUS study, respectively, and corresponding maxima of 7 and 43 patients. The
Table I. Patient matching

<table>
<thead>
<tr>
<th>Study group (n = 101)</th>
<th>Bare control group (n = 323)</th>
<th>P*</th>
<th>Cypher control group (n = 350)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y; mean ± SE)</td>
<td>61.1 ± 1.1</td>
<td>.1216</td>
<td>62.6 ± 1.1</td>
<td>.2236</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>74 (73.3)</td>
<td>213 (65.9)</td>
<td>1253</td>
<td>255 (72.9)</td>
</tr>
<tr>
<td>Prior infarction [n (%)]</td>
<td>47 (46.5)</td>
<td>93 (29.1)</td>
<td>.0013</td>
<td>100 (29.4)</td>
</tr>
<tr>
<td>Prior bypass surgery [n (%)]</td>
<td>5 (5.0)</td>
<td>33 (10.2)</td>
<td>.0810</td>
<td>34 (9.7)</td>
</tr>
<tr>
<td>Diabetes mellitus [n (%)]</td>
<td>27 (26.7)</td>
<td>97 (30.0)</td>
<td>95 (27.1)</td>
<td>.1801</td>
</tr>
<tr>
<td>Hyperlipidemia [n (%)]</td>
<td>83 (82.2)</td>
<td>235 (73.4)</td>
<td>.0876</td>
<td>256 (74.6)</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>62 (61.4)</td>
<td>214 (66.5)</td>
<td>.0876</td>
<td>256 (74.6)</td>
</tr>
<tr>
<td>Smoking [past year; n (%)]</td>
<td>36 (36.0)</td>
<td>79 (24.7)</td>
<td>.0243</td>
<td>70 (20.2)</td>
</tr>
<tr>
<td><strong>Angiographic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preprocedural</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD [n (%)]</td>
<td>50 (49.5)</td>
<td>153 (47.7)</td>
<td>.9277</td>
<td>163 (46.6)</td>
</tr>
<tr>
<td>Type C [n (%)]</td>
<td>23 (22.8)</td>
<td>48 (14.9)</td>
<td>.5379</td>
<td>80 (22.9)</td>
</tr>
<tr>
<td>Thrombus present [n (%)]</td>
<td>11 (10.9)</td>
<td>3 (0.9)</td>
<td>&lt;.0001</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>MLD in-lesion (mean ± SE)</td>
<td>0.72 ± 0.03</td>
<td>0.88 ± 0.02</td>
<td>.0040</td>
<td>0.82 ± 0.02</td>
</tr>
<tr>
<td>RVD in-lesion (mean ± SE)</td>
<td>2.36 ± 0.01</td>
<td>2.42 ± 0.01</td>
<td>†</td>
<td>2.41 ± 0.01</td>
</tr>
<tr>
<td>Lesion length (mean ± SE)</td>
<td>14.5 ± 0.3</td>
<td>14.4 ± 0.2</td>
<td>†</td>
<td>14.6 ± 0.2</td>
</tr>
<tr>
<td><strong>Postprocedural</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stent length (mean ± SE)</td>
<td>24.4 ± 0.7</td>
<td>23.0 ± 0.5</td>
<td>1254</td>
<td>23.6 ± 0.6</td>
</tr>
<tr>
<td>RVD (mean ± SE)</td>
<td>2.39 ± 0.02</td>
<td>2.51 ± 0.01</td>
<td>&lt;.0001</td>
<td>2.51 ± 0.01</td>
</tr>
<tr>
<td>MLD (mean ± SE)</td>
<td>2.18 ± 0.02</td>
<td>2.39 ± 0.02</td>
<td>&lt;.0001</td>
<td>2.41 ± 0.02</td>
</tr>
<tr>
<td>Stents implanted (n; mean ± SE)</td>
<td>1.15 ± 0.05</td>
<td>1.43 ± 0.04</td>
<td>&lt;.0001</td>
<td>1.48 ± 0.04</td>
</tr>
<tr>
<td>In-stent DS (%; mean ± SE)</td>
<td>7.8 ± 0.8</td>
<td>4.4 ± 0.5</td>
<td>.0004</td>
<td>3.5 ± 0.5</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; DS, diameter stenosis.
*Study group compared with bare control.
†Study group compared with Cypher control.
Matching criteria:

- Statistical analysis plan, including the matching process, was prepared before QCA or IVUS data were available. The primary comparison between the Cypher stent and the bare stent was tested by analysis of variance performed on 8-month follow-up data. A test of superiority (two-sided: α = .05, power ≥95%) assumed that the Cypher stent would be more effective than the bare stent. The threshold of clinical relevance was a mean reduction of 0.20 mm in-lesion late lumen loss. The Cypher stent in the Svelte study (study group) and Cypher stents in the SIRIUS (Cypher control group) were compared on the primary outcome variable but with a test of noninferiority (one-sided test: α = .05, power ≥85%) which assumed that the standardized procedure would be at least as effective as customary practices. Adverse events were analyzed using the actuarial life table method, with survival estimates using Kaplan-Meier methods and survival comparisons using the Peto-Peto function. Lastly, univariate and stepwise multivariate analyses were performed on all variables to determine prognostic factors and included blocks. Odds ratios were calculated using the Mantel-Haenszel method. All statistical analyses were performed with SAS software (version 8.02) (SAS Institute Inc, Cary, NC).

**Results**

Actual target vessel diameters ranged from 1.70 to 3.03 mm in study patients and control subjects. Table I shows that groups were well matched in the 3 variables that defined blocks (diabetes mellitus, RVD, and lesion length).

In-lesion and in-stent MLD values of patients with and those without diabetes were almost identical immediately postprocedure; however, 8 months later, the angiographic follow-up data were less satisfactory for patients with diabetes, confirming the known poorer outcomes of the population with diabetes. Mean in-lesion late loss in patients with diabetes (0.32 ± 0.46 mm) was almost twice that of patients without diabetes (0.16 ± 0.35 mm), and in-stent late loss was greater (0.27 ± 0.40 mm vs 0.20 ± 0.35 mm, respectively). In-lesion MLD was reduced in patients with diabetes (1.57 ± 0.34 mm vs 1.71 ± 0.35 mm, respectively); in-lesion restenosis >50% was more frequent (12.5% vs 4.2%, respectively), as was in-stent restenosis (4.2% vs 2.8%, respectively); and neo-intimal volume was greater (2.08 vs 1.71 mm³, respectively). Fewer patients with diabetes avoided TVR (89.3% vs 95.6%, respectively) or MACE (85.6% vs 97.3%, respectively).

Univariate and multivariate analyses were applied to the Cypher stent QCA data of this cohort at 8 months. In-lesion late loss was predicted by univariate analyses, which showed significant positive relationships with postprocedure RVD, postprocedure in-stent MLD, pre-procedure RVD, and a history of diabetes. Multivariate analyses revealed significant positive relationships with postprocedure in-stent MLD and total stent length. The factor total stent length significantly predicted all
secondary variables (Table II) in the univariate and multivariate analyses.

Significant group differences were present regarding prior myocardial infarction, cigarette smoking during the past year, thrombus and MLD, as well as both postproce-
dure RVD and in-stent diameter stenosis and were slightly
to the disadvantage of the patients in the study group.
Slightly more stents were implanted in the control
to the disadvantage of the patients in the study group.

Comparison with bare control subjects

Immediate and follow-up results are shown in Table II. Angiographic data at 8 months were available for 94% of the patients (95/101) treated in the study group and for 66% of the subjects (213/323) treated in the bare control group.

Postprocedure, mean in-lesion MLD in the study group
(1.9 mm) was significantly smaller than that in the bare control group (2.1 mm) (Table II). This reflects the

Comparison with Cypher control subjects

Table I shows that the patients treated with the
Cypher stent in this study group or in the Cypher control group were well matched (diabetes mellitus, RVD, and lesion length).

The slight mismatches regarding prior myocardial infarction, prior bypass surgery, smoking during the past year, lesion location, American College of
Cardiology/American Heart Association (ACC/AHA) lesion class, presence of preprocedure thrombus, preprocedure MLD, and 2 postprocedure variables (RVD and in-stent diameter stenosis) disadvantaged patients of the study group. The number of Cypher stents implanted was slightly higher in the SIRIUS cohort than in this study, although mean stent length was similar in all groups.

Immediately postprocedure, lesion success, device success, and procedure success were attained for virtually all matched patients (N = 451) with both the study and Cypher control groups (Table II). Angiographic data at 8 months were available for 94% of the patients (95/101) treated in the study group and for 66% of the subjects (232/350) treated in the Cypher control group.

The mean in-lesion late loss (primary efficacy variable) was similar for both groups. Target lesion revascularization rates were slightly lower in the study group and approached statistical significance (P = .0125). Table II shows that the study group was not inferior in efficacy to the Cypher control group.

**Intravascular ultrasound results**

Intravascular ultrasound was performed on 100 patients postprocedure in the study group, but only 76 assessments could be analyzed. At 8 months, 91 assessments were performed and 66 assessments were analyzed (Table III). At 8 months, there was a statistically significant (P < .0001) reduction in the neointimal hyperplasia area in the study group as compared with the control groups.

**Clinical events**

Adverse events up to 12 months were rare. There were 2 cases of non-Q-wave myocardial infarctions and 3 major bleeding complications in the study group before hospital discharge. Three deaths (3%) and 1 Q-wave myocardial infarction (not involving the target lesions) occurred out of the hospital setting. There had been 4 deaths (1.2%) in the bare control group and 5 (1.4%) in the Cypher control group. The respective frequencies for myocardial infarction were as follows: study group, 3.0%; bare control group, 3.1%; Cypher control group, 2.8%.

**Repeat interventions**

Repeat interventions were performed in 3.0% of the study group and in 22.0% of the bare control group (P < .0001) and 5.7% of the Cypher control group (P = .1156).
Discussion

The angiography and ultrasound results of all efficacy variables confirmed the findings of the subgroup analysis of the SIRIUS trial showing the Cypher stent to be superior to the bare stent in small coronary arteries at high risk of restenosis. The comparison with the Cypher control group fell within the margin of clinical equivalence, with the mean in-lesion late loss (primary efficacy variable) found to be similar for both groups. The IVUS results showing a statistically significant reduction in the neointimal hyperplasia area in the study group as compared with the control groups suggest that the more rigid implantation policy used in the SVELTE study may have improved outcomes. The study also confirmed the improvements achieved with the Cypher stent versus bare metal stents in patients with diabetes.

These findings are similar to those of other randomized controlled trials showing the efficacy of drug-eluting stents in small coronary arteries. In the E-SIRIUS trial, patients with de novo lesions (mean vessel diameter 2.55 mm) randomized to treatment with sirolimus-eluting stents had improved outcomes compared with patients treated with bare metal stents: at 8 months, the minimum lumen diameter was significantly higher and restenosis was significantly lower in the sirolimus-eluting stent–treated patients. In the C-SIRIUS trial (based on the same protocol as that observed in the E-SIRIUS trial), at 8 months, MLD was significantly higher and TVR was significantly lower in small native coronary arteries implanted with a sirolimus-eluting stent as compared with the control subjects treated with a bare metal stent. In the SES-SMART trial, the mean vessel diameter was even smaller at only 2.2 mm, but the efficacy outcomes at 8 months with the sirolimus-eluting stent were similar to those in the abovementioned studies, with significant reductions in restenosis rates and MACEs.

However, recent data from the e-Cypher registry, designed to assess sirolimus-eluting stent performance in a real world setting, were not as favorable in small vessels with a diameter ≤2.5 mm. At 180 days, stent thrombosis and MI were higher compared with larger vessels whereas MACEs and TLR were similar in both groups. Results of the RESEARCH registry showed low rates of angiographic and clinical complications in very small vessels stented with 2.25 mm of sirolimus-eluting stent, although the MLD was significantly lower compared with stents in larger vessels. The long-term outcomes of such registries, together with improvements in angiographic follow-up rates, will help confirm the effectiveness of sirolimus-eluting stents in small vessels shown in randomized controlled trials.

Study limitations

The study had some limitations because of its non-randomized nature, limited sample size, and the use of historical control groups from the SIRIUS trial, conducted at centers other than those of the present trial. At 8 months of follow-up, angiographic data were only available from 66% of both the bare control and Cypher control groups as compared with 94% of patients in the study group. For the IVUS comparisons at 8 months, data were available from 65% of patients in the study group as compared with only 12% and 20% of the bare control and Cypher control groups, respectively. These significant differences in follow-up rates make it difficult to fully compare the outcomes between the groups. However, patients were matched on 3 major variables (diabetes, RVD, and lesion length), which disadvantaged the study group in variables where they were not well matched.

Conclusions

The sirolimus-eluting Cypher stent is confirmed to be superior to the bare Bx Velocity stent in terms of in-lesion late loss at 8 months in small coronary vessels with a high risk of restenosis. Procedural rigor may have helped decrease the in-lesion late loss assessed by IVUS and the need for TLR.

References


